REMARKS

I. Introduction

Applicant acknowledges receipt of the April 18, 2011 Office Action. In the Office Action, the Examiner has objected to the specification for containing uncapitalized trademarks. The Examiner has also rejected claims 85-93, 96-103, 109-113, 116 and 124-128 under 35 U.S.C. 112, second paragraph, for allegedly being indefinite.

The Examiner further rejected the following claims for allegedly being obvious:

(1) Claims 109-113 over Catchpole (WO 02/36792) in view of Nott et al. (RNA, 2003).

(2) Claims 124-128 over Bulla (J. Virol., 1998) in view of Protzer et al. (PNAS, 1999) and Catchpole.

(3) Claims 85-93 and 96-102 over Catchpole, in view of Nott, Thudium (WO 02/031137), Li et al. (Gene Therapy, 2001), Ivy (US Patent 6165477), and Palmiter et al. (PNAS 1991), as further evidenced by GenBank Accession AF143308, Asselbergs (PGPUB 20030124523) and Renner (PGPUB 2003175711).

(4) Claim 103 over the combination of Catchpole, Nott, Thudium, Li, Ivy, Palmiter, GenBank Accession AF143308, Asselbergs, and Renner, in view of Scharton-Kerten et al. (Infection and Immunity, 2000).

Additionally, the Examiner issued a provisional non-statutory obviousness type double patenting rejection against claims 85-93, 96-103, 109-113, 116 and 124-128 over claims 115-123, 126, 132-133, 137-156 of copending U.S. Application No. 11/815,278.

Applicant respectfully requests reconsideration of the present application in view of the forgoing amendments and in view of the reasons that follow.

II. Status of the Claims

Claims 1-84 are canceled. Claims 94, 95, 104-108, 114-115, 117-123, 129 and 130 are withdrawn. Claims 85, 109, 116 and 124 are currently amended. Support for the amendments can be found, for example, at page 23, lines 10-12 and page 25, lines 20-24 of the specification and in Figures 8 through 12. Support for claims 131-132 can be found in the specification on page 5 at line 5. Claims 85-93, 96-103, 109-113, 116, and 124-128 and 131-132 are currently pending and under review.

III. Objection to the Specification

The Examiner objects to the specification for failing to capitalize trademarks, including QUANTUM II, TWEEN, LIPOFECTION, etc. Applicant amends the specification to capitalize all trademarks and accompany the trademarks with corresponding generic terminologies. Applicant therefore respectfully requests that the objection be withdrawn.

IV. Rejections under 35 U.S.C. 112

(1) "in place of intron A"

The Examiner has rejected claims 85-93, 96-103, 109-113 and 116 as allegedly being indefinite. The Examiner has indicated that that "if a heterologous intron were to be provided *in place of* the intron A region as claimed, it would not be possible for the heterologous intron not to be positioned between exons 1 and 2." Office Action, page 3, paragraphs 1 and 2, emphasis added.

Applicant submits that the phrase "in place of the intron A" means that the claimed chimeric promoter contains a heterologous intron instead of a full length native intron A of the hCMV major immediate early gene. The phrase "in place of the intron A" does not mean that the heterologous intron must be positioned between exons 1 and 2. *See, e.g.*, Figures 8 through 12, wherein the chimeric promoter comprises (1) CMV exons 1 and 2 located directly adjacent to one another, and (2) a heterologous intron (e.g., rat insulin intron A) that is not located between exons 1 and 2. Additional disclosure about the meaning of the phrase can be found in the specification as filed, on page 23, line 10-12 ("In the present chimeric construct

exon 2 sequence is generally positioned 3' of exon 1 sequence, without intervening intron sequence, so that the exon 1 and exon 2 sequences are contiguous."); page 25, line 20-21 ("A heterologous intron is one which is not present in the coding sequence in nature"); and page 25, line 22-24 ("The heterologous intron (c) replaces wholly or partially, native intron A of the hCMV major immediate early gene. Typically the native intron is absent.").

In the interest of expediting prosecution of this application, without acquiescing to the Examiner's rejection, however, Applicant amends claims 85, 109 and 116. Specifically, Applicant deletes the phrase "provided in place of the intron A region of the hCMV major immediate early gene" and adds "and wherein the chimeric promoter sequence does not comprise the native intron A region of the hCMV major immediate early gene."

(2) "3' of ... the coding sequence"

The Examiner has rejected claims 124-128 for allegedly being indefinite based on language relating to "3'" recited in independent claim 124. In the interest of expediting prosecution of this application without acquiescing to the Examiner's rejection, Applicant herein amends (iii) in claim 124 to recite "an enhancer sequence located downstream of the coding sequence (ii)," and later recite "enhancer sequence (iii)" in the last "wherein" clause. Applicant believes such claim language is consistent with the Examiner's interpretation as stated on page 4 of the Office Action, lines 16-17.

Applicant respectfully requests that the Examiner withdraw the above-mentioned indefiniteness rejection.

V. Rejections under 35 U.S.C. 103

(1) Rejection over Catchpole in view of Nott and Thudium

The Examiner has rejected claims 109-113 and 116 as allegedly being obvious over Catchpole in view of Nott and Thudium. The Examiner asserts that Catchpole teaches DNA vectors "include[ing] exon 1 and a heterologous intron that replaces the natural intron A" and "further ... including a part of exon 2." Office Action, page 5. The Examiner acknowledges that Catchpole does not teach positioning a heterologous intron anywhere other than between

exons 1 and 2. The Examiner asserts nonetheless that it would have been obvious for one of ordinary skill in the art to vary the position of an intron because Nott "teach[es] that varying the position of a single intron leads to differential expression of a gene." Office Action, page 6. Applicant respectfully traverses this rejection.

Unlike the present invention where the intron is part of the chimeric promoter located outside the coding sequence, Nott only teaches inserting a intron into one of two different positions ***inside*** the *Renilla* luciferase ***open reading frame*** (ORF). To optimize intron excision with "the context of ... naturally flanking exons," Nott flanks the intron with "exons 6 and 7 ... [in] the *Renilla* ORF," resulting in the production of a fusion protein, instead of an intact desired protein.

Unlike the teachings in Nott, the recited intron in the present invention is part of the chimeric promoter, i.e., outside the ORF, thereby enabling the construct in the present invention to express intact proteins, not fusion proteins from ORFs comprising the recited intron itself. Nott's teaching of inserting an exon-flanked intron into the ***open reading frame*** of an encoded protein to produce a fusion protein would in no way motivate or suggest Applicant's invention. Nothing in Nott suggests to one skilled in the art to create a nucleic acid construct comprising ***a chimeric promoter*** comprising a CMV promoter sequence, exon 1 and at least part of exon 2, and a heterologous intron as claimed in the present invention, much less such a promoter where the heterologous intron is not located between exon 1 and 2.

Moreover, Catchpole itself teaches away from a combination with Nott. As the Examiner acknowledges, Catchpole does not teach positioning a heterologous intron anywhere other than between exons 1 and 2. The Examiner asserts that Nott cures Catchpole's deficiency because Nott teaches that varying the position of a single intron affects the expression of a gene. Catchpole teaches, however, that the promoter disclosed there (which has the heterologous intron *between* exons 1 and 2) has "enhanced expression." Catchpole, page 2, line 4. In other words, Catchpole teaches that this exact location of the heterologous intron is important for enhanced expression in Catchpole's construct, and nothing in Nott suggests otherwise. In fact, nothing in Nott suggests that there would be any benefit in altering the location of an intron located between exons 1 and 2 in Catchpole's

constructs, or that moving just any intron would necessarily result in a viable expression construct. Thus, contrary to the Examiner's assertion, Catchpole would discourage a person skilled in the art from applying the teaching of Nott to vary the intron position in Catchpole's construct.

Thudium fails to cure the deficiencies of Catchpole and Nott. Even assuming Thudium discloses a method for isolating/purifying DNA constructs, nothing in this reference suggests a chimeric promoter comprising a CMV promoter sequence, exon 1 and at least part of exon 2, and a heterologous intron as claimed in the present invention, much less such a promoter where the heterologous intron is not located between exon 1 and 2.

Thus, the cited references, either alone or in combination, fail to teach or suggest a construct with a chimeric promoter comprising a heterologous intron along with exons 1 and 2 of the hCMV major immediate sequence early gene, much less that the intron is not located between exons 1 and 2. Applicant therefore respectfully requests that the Examiner withdraw the obviousness rejection.

(2) Rejection over Bulla in view of Protzer and Catchpole.

The Examiner has rejected claims 124-128 for allegedly being obvious over Bulla in view of Protzer and Catchpole. The Examiner asserts that Bulla disclose "a nucleic acid construct comprising a promoter sequence and an enhancer sequence derived from 3' UTR of the HBsAg gene." Office Action, page 8. The Examiner acknowledges that Bulla "do[es] not teach a coding sequence that is heterologous to the 3' UTR enhancer sequence." Office Action, page 8. In other words, the Examiner acknowledges that Bulla does not teach replacing the "HBsAg coding sequence" in its construct with a heterologous coding sequence. Abstract and page 1437 column 2.

The Examiner alleges, however, that it would have been obvious for one skilled in the art "to incorporate a heterologous coding sequence... such as interferon, as a substitute coding sequence [to replace the HBsAg coding sequence] in the construct taught by Bulla" because "Protzer et al disclose the gene transfer of interferon." Office Action, page 8. Applicant respectfully traverses this ground of rejection.

Contrary to the Examiner's assertion, Protzer does not teach substituting the HBsAg coding sequence in Bulla's construct with a heterologous coding sequence. Indeed, Protzer actually teaches away from using a heterologous coding sequence to replace the HBsAg coding sequence. As Protzer makes clear, among the different gene segments that Protzer attempted to substitute with a heterologous coding sequence, "only substitution of the small envelope (S) gene by foreign [i.e., heterologous] sequences turned out to be successful." Protzer, page 10820, end of paragraph spanning cols 1 and 2 . Thus, Protzer taught that one should substitute a heterologous coding sequence for the small envelope (S) gene in a relevant construct, and not other genes, which Protzer tried and failed. Led by Protzer, therefore, a skilled artisan would not have replaced the HBsAg coding sequence in Bulla with a heterologous coding sequence to arrive at the present invention.

Nothing in Protzer nor Bulla, other alone or combined, suggests a construct comprising an enhancer sequence located downstream of a coding sequence, where the coding sequence is heterologous to the enhancer sequence. In Bulla, the coding sequence is not heterologous to the enhancer sequence, and nothing in this reference suggests that a hepatitis B virus enhancer should be paired with any sequence other than the hepatitis B virus surface antigen (HBsAg) gene. Along the same lines, Protzer, who tried to substitute a heterologous coding sequence in hepatitis B virus plasmids, and took care "not to affect cis-acting control elements" such as enhancers, failed to get such a plasmid to work unless one substituted one specific gene, i.e., a gene other than the HBsAg gene. Thus, one had no reason to substitute the HBsAg gene with a heterologous coding sequence. Neither Bulla nor Protzer indicated that such a substitution would be "successful" when preparing the type of plasmids disclosed in either reference.

In the Office Action on page 8 relating to this rejection, the Examiner only asserts that Catchpole teaches coating a nucleic acid vector onto a gold bead and other information relevant to needle-free delivery. Nothing in Catchpole cures what is lacking in Bulla and Protzer as discussed above, and the Examiner does not allege otherwise.

Thus, the cited references, either alone or in combination, fail to teach or suggest an enhancer sequence located downstream of a heterologous coding sequence to arrive at the present invention. Applicant therefore respectfully requests that this rejection be withdrawn.

(3) Rejection over Catchpole in view of Nott, Thudium, Li, Ivy, Palmiter, Genbank Accession number AF143308, Asselbergs and Renner.

The Examiner has rejected claims 85-93 and 96-102 as allegedly being obvious over Catchpole in view of Nott , Thudium, Li., Ivy, Palmiter, Genbank Accession number AF143308, Asselbergs and Renner. While acknowledging that Catchpole does not teach using a heterologous intron that is not positioned between exons 1 and exon 2, the Examiner asserts that it would have been obvious for one of ordinary skill in the art to vary the position of an intron because Nott "teach[es] that varying the position of a single intron leads to differential expression of a gene." Office Action, page 6. Applicant respectfully traverses this rejection.

As discussed above in (1), unlike the present invention where the intron is part of the chimeric promoter located outside the coding sequence, Nott only teaches inserting an intron into one of two different positions ***inside*** an ***open reading frame***. To optimize intron excision with "the context of ... naturally flanking exons," Nott flanks the intron with "exons 6 and 7 ... [in] the *Renilla* ORF," resulting in the production of a fusion protein, instead of an intact protein.

None of the other cited references cure Catchpole's deficiency. Palmiter suffers the same deficiency as Nott because it does not teach a chimeric promoter comprising a heterologous intron, i.e., where the heterologous intron is part of the promoter. Palmiter only teaches placing an intron "within (or [d]ownstream of) the ... rGH gene" or "between the mMT-I promoter and the rGH gene." Palmiter, page 480, column 1 and page 479, column 1, respectively. Nothing in Palmiter teaches or suggests a chimeric promoter comprising a heterologous intron, much less a chimeric promoter comprising an hCMV immediate early promoter sequence, exon 1 and at least part of exon 2 of the hCMV major immediate early gene, and a heterologous intron that is not positioned between exons 1 and 2.

Likewise, nothing in Li, Ivy, Asselbergs and/or Renner teaches or suggests a chimeric promoter comprising a heterologous intron, much less the promoter of Applicant's invention as discussed above. Thus, the cited references, either alone or in combination, do not teach a chimeric promoter comprising an hCMV immediate early promoter sequence and a heterologous intron that is not positioned between exons 1 and 2 of the hCMV major immediate early gene. Applicant therefore respectfully requests that the obviousness rejection be withdrawn.

(4) Rejection over the combination of Catchpole, Nott, Thudium, Li, Ivy, Palmiter, Genbank Accession number AF143308, Asselbergs and Renner in view of Scharton-Kersten.

The Examiner has rejected claim 103 as allegedly being obvious over the combination of Catchpole, Nott , Thudium, Li, Ivy, Palmiter, Genbank Accession number AF143308, Asselbergs and Renner in view of Scharton-Kersten.

Applicant's above remarks in (1) and (3) also apply to this rejection. While acknowledging that Catchpole does not teach using a heterologous intron that is not positioned between exons 1 and exon 2, the Examiner relies on Nott to cure Catchpole's deficiency. Yet, unlike the present invention where the intron is part of the chimeric promoter located outside the coding sequence, Nott only teaches inserting a intron into one of two different positions ***inside*** an open reading frame.

As discussed above, Li, Ivy, Palmiter, Asselbergs and/or Renner do not cure Catchpole's deficiency. Likewise, Scharton-Kersten fails to cure Catchpole's deficiency because Scharton-Kersten does not discuss introns at all. Thus, the cited references, either alone or in combination, do not teach Applicant's chimeric promoter comprising an hCMV immediate early promoter sequence and a heterologous intron that is not positioned between exons 1 and 2 of the hCMV major immediate early gene. Applicant therefore respectfully requests that the obviousness rejection be withdrawn.

VI. Double Patenting Rejection

The Examiner has provisionally rejected claims 85-93, 96-103, 109-113, 116, 124-128 as being unpatentable over claims 115-123, 126, 132-133, 137-156 of copending Application No. 11/815, 278. Applicant respectfully requests that the Examiner hold the provisional double-patenting rejection in abeyance pending indications of allowable subject matter in the current and other pending application, at which time the Applicant respectfully requests that the Examiner contact the undersigned to discuss options to overcome the rejection.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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